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Social support decreases depressogenic effect of low-dose interferon alpha treatment in melanoma patients

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ABSTRACT

Objective: The most frequent serious psychological side effect of immune therapies is depression. In the present study, we tested whether social support, as a positive environmental effect, is able to moderate depression or anxiety symptoms in melanoma patients during adjuvant low-dose interferon treatment.
Methods: Hundred and twenty-seven melanoma patients with negative psychiatric history were included in our longitudinal study and followed up for one year. Depression and anxiety symptoms were measured six times during treatment: at baseline, at 1st, 3rd, 6th, 9th and 12th month of the therapy. In addition, social support was investigated with the Social Dimension Scale.
Results: Depressive symptoms significantly increased during the 12-month follow-up period ($p < 0.001$). However, social support significantly moderated the depressogenic effect of low-dose interferon treatment ($p < 0.001$). Patients with better social support showed attenuated increase of depression. Anxiety showed no significant changes during the low-dose interferon treatment ($p = 0.230$). Social support had no moderating effect on anxiety symptoms ($p = 0.745$) during the follow up.
Discussion: Our data provide evidence that social support and interferon alpha treatment significantly interact in the development of depression. In addition, our study emphasises that enhancement of social support can reduce depressogenic side effects and increase compliance during adjuvant interferon treatment, and thus, psychological screening and psychooncological counselling should be incorporated in the treatment protocol.

Introduction

90% of melanomas are diagnosed as primary tumours without metastasis and for patients with early-stage non-metastatic disease surgical management remains the mainstay of therapy [1]. Adjuvant immunotherapy is offered to those melanoma patients who have no evidence of metastases but at high risk for further tumour spread, e.g. with tumours thicker than 1.5 mm, or in stage II and III melanoma. Specifically, interferon alpha is the fundamental therapy as it was the first substance in the adjuvant treatment of melanoma to have shown a significant improvement of disease-free survival [2,3]. However, adjuvant interferon treatment is frequently accompanied by psychological side effects including depression, fatigue, irritability, anxiety, or suicide.

The incidence of clinically relevant depression during interferon therapy varies between 20% and 40% [4,5] making it the most common side effect and one of the main reasons for early discontinuation of treatment [3]. Depressive or anxiety disorders in the psychiatric history increase the risk of psychiatric side effects during treatment. In addition, female sex, younger age, lower education, and lack of social support were investigated as risk factors for evolving psychiatric side effects, but conclusive biological or psychological markers predicting psychological side effects of interferon treatment are lacking [4]. Thus, routine monitoring of melanoma patients remains to identify clinically relevant psychological distress and possible protective factors [6].

The exact mechanism of interferon action on the central nervous system is not well understood although several hypotheses have been investigated [2,7]. Previous studies demonstrated that inflammatory cytokines are able to induce neuropsychiatric symptoms such as sickness behaviour in animals or depression in humans, possibly by increasing

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hypothalamic-pituitary-adrenal (HPA) axis activity or by decreasing monoamine neurotransmitter concentration in the brain [5,7]. However, it is important to note that both cytokine synthesis and HPA activity are heavily influenced by acute and chronic environmental stressors [8]. Thus, factors that can alleviate environmental stress may have a beneficial consequence on psychological side effects of low-dose interferon treatment by modulating overlapping biological mechanisms.

Social support, the presence of significant others who are able to provide psychological or physical help in need may modify the effects of negative life events in the development of depression [9]. For example, in a natural disaster-exposed population the short allele of the serotonin transporter gene 5-HTTLPR polymorphism which was associated with depression vulnerability after negative life events [10] only increased risk of depression if social support was low [11]. Lack of social support was also a potential factor for non-remission after depressive episodes [12]. In addition, social support is an influential factor in adjustment to cancer. Greater social support was associated with better mood, with less mood disturbance, and with better emotional control. Talking about traumatic experiences with an empathic and supportive other may promote adaptation by facilitating adaptive cognitive processing of stressful or traumatic events [13]. In addition, social support decreased HPA reactivity and cytokine response in experimental studies [14].

In the present study, our primary aim was to investigate the psychological side effects of low-dose interferon treatment in melanoma patients. Specifically, we tested the protective effect of social support on psychological side effects elicited by the increased activity of the pro-inflammatory cytokine pathway, such as depression and anxiety. We hypothesised that greater social support will be associated with better adjustment, namely less depressive and anxiety symptoms during treatment.

Method

At the Department of Oncodermatology in the National Institute of Oncology (Hungary) 127 patients were recruited for this open-label follow-up study. All patients signed informed consent to participate in the study which was approved by the Ethics Committee of the National Institute of Oncology, and the study was carried out in accordance with the Declaration of Helsinki.

Inclusion criteria were tumour thickness of 1.5 mm or thicker, no evidence of regional or distant metastases, except micrometastases in the sentinel lymph nodes. Exclusion criteria were mucosal or ocular melanoma, pregnancy, breast-feeding, autoimmune diseases and pre-existing Axis I or Axis II psychiatric disorders. All patients were recruited within 8 weeks after surgery for malignant melanoma. They received interferon alpha 2a in a weekly dose of 3×3 MIU/week subcutaneously and regularly attended control examinations at month 0, 1, 3, 6, 9, and 12.

All subjects completed a psychological questionnaire booklet at least three times during the first year of therapy. Questionnaires were filled out at outpatient clinics during the regular visits.

Questionnaires

Demographic data, such as sex, age, home, family and financial status, and level of education were measured by a standardised background questionnaire regularly used in our institute [15]. Financial status was categorized with a single question “How well do you feel you are managing financially these days?” and was subjectively rated by the participant on a 5 item Likert scale ranging from very bad (0) to very good (4).

The Beck Depression Inventory [16] was used to detect symptoms of depression. The BDI is a 21-item self-report questionnaire that assesses the severity of an individual's depressive symptoms. Sum of the item scores was used in the analysis. The BDI was validated in the Hungarian population and the cut-off score for minor depression was 14 (SD = 4) and for clinical relevant depression 27 [17].

The State-Trait Anxiety Scale (STAI) was used to measure anxiety symptoms. The STAI-State subscale presents 20 items describing anxiety states for which the patient selects one of four descriptors that best represents his/her feelings [18]. Sum of the item scores was used in the analysis. The STAI-State was validated in the Hungarian population and the cut-off score for clinical anxiety was 38.40 (SD = 10.66) in men and 42.64 (SD = 10.79) in women [19].

Social support was measured with the Social Dimension Scale developed by Caldwell et al. [20]. This scale was validated for the Hungarian population by Kopp et al. [21]. Patients rated their subjective relationships with important others from 0 to 3. Sum of the item scores was used in the analysis.

Other measures

The data of thickness and invasion of primary tumour (Breslow's depth and Clark invasion) were determined with histopathological examinations following the national standards of care [1,23,24]. Breslow's depth is a measure of cell invasion into the skin in millimetres in case of malignant melanomas. Clark invasion describes the level of anatomical (e.g. epidermis, dermis or fat) invasion of skin melanomas. Besides ulceration (defined by interruption of the surface epithelium by tumour cells) and mitotic rate, Breslow's depth is the most important prognostic factor in the melanoma classification system recommended by the American Joint Commission on Cancer (AJCC) and Clark's level has far less importance [22,23].

Statistics

Data were analysed by SPSS 21 for Windows (IBM). The measured psychometric scores showed normal or F-distribution in our samples (Kolmogorov–Smirnov and Shapiro–Wilk tests). Baseline between-group comparisons were evaluated by t-tests (continuous variable) and by chi-square tests (nominal and ordinal variables; Pearson Chi-Square and Likelihood Ratio) for independent samples. Repeated measure of ANCOVA was used to analyse the effect of interferon treatment during the follow-up on psychometric measures. In all ANCOVAs Greenhouse–Geiser correction was applied and age, sex, financial status, social support, education and tumour thickness (Breslow) were co-variants. The level of significance was $p = 0.05$, two-tailed. To test the longitudinal effect of interferon treatment on BDI depression score we used repeated measure of ANCOVA with sex, age, financial status, education, and social support as covariates in the model. As vertical tumour thickness (Breslow's depth) is the most important histological prognostic factor for primary melanoma [1] this was also included in the model as covariate.

Results

Description of the study population can be seen in Table 1. None of the patients had depression or anxiety scores above the Hungarian cut-off score for clinical depression or anxiety at the beginning of the study.

Baseline

At baseline, there were significant differences in BDI depression scores according to education, financial status, and sex (Table 2). Higher educated patients, patients with better financial conditions and male patients scored lower on BDI compared to the other group. There were no significant differences in BDI depression scores at baseline according to social support, family status or tumour parameters (Breslow's depth, exulceration of primary tumour, or Clark's level of invasion groups).

At baseline, there were significant differences in STAI-State anxiety scores according to sex and financial status (Table 3). Women and subjects with very bad or bad financial situations scored higher on the STAI-State anxiety subscale at baseline compared to the other groups. There were no significant differences according to other investigated factors.

Longitudinal effect of interferon treatment on depression

In the study group, BDI depression scores steadily and significantly increased during the treatment (Fig. 1). Among the investigated co-variants only social support showed a